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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/648,304	08/25/2000	Airton Monza da Silveira	1369-00	6411

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EXAMINER
PULLIAM, AMY E

ART UNIT	PAPER NUMBER
1615	18

DATE MAILED: 04/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/648,304	SILVEIRA ET AL.	
	Examiner	Art Unit	
	Amy E Pulliam	1615	

-- Th MAILING DATE of this communication appears on th cov r sh et with the corr spond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of Papers

Receipt is acknowledged of Request for Extension of Time, the Amendment C, and the Information Disclosure Statement, all received by the Office January 21, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, and 4-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Us Patent 5,932,248 to Chen *et al.* in view of US Patent 5,246,611 to Trinh.

Chen *et al.* disclose a controlled release preparation comprising an ionic polymer matrix loaded with an active compound, wherein the active compound is a cytotoxic or cytostatic drug, and the active compound is complexed with a complexing agent in order to modify the release of the active from the polymer matrix (abstract). Chen *et al.* also teach doxorubicin as an exemplary active ingredient (c 14, claim 4). Chen *et al.* further teach that the ionic polymer matrix can be provided in the form of many types of formulations, including nanoparticles (c 3, l 46-50). However, Chen *et al.* do not teach cyclodextrin as the complexing agent.

Trinh discloses cyclodextrin complexes. However, the disclosure of Trinh is relied upon for the teaching that cyclodextrin and its derivatives are very well known to act as complexing agents (c 1, l 25-55). Furthermore, Trinh teaches that the teachings of cyclodextrins inclouds

alpha, beta, and gamma-cyclodextrins, and their derivatives, which are all known complexing agents.

It is the position of the examiner that one of ordinary skill in the art would have been motivated to use a different and known complexing agent in the formulation disclosed by Chen *et al.*, as Chen *et al.* disclose that this is acceptable, and particularly because Trinh *et al.* teach that cyclodextrins are so well known as complexing agents. The expected result would be successful micro or nanoparticle formulation with an active cytotoxic agent complexed by a well known complexing agent.

Additionally, the combination of references does not specifically teach each active agent claimed by applicant, nor does it teach the specific particle sizes and weight percents of the formulation components. First, it is the position of the examiner that applicant has placed no criticality on the specific drug, and therefore, any drug could benefit from the controlled release preparation. Absent any evidence to the contrary, it is the position of the examiner that one of ordinary skill in the art would have been motivated to use any well known drug, which would benefit from controlled properties, particularly because Chen *et al.* teach the use of cyctotoxic drugs such as doxorubicin.

Second, absent evidence of criticality stemming directly from these limitations, the particular particle size and weight percents are not found to render patentable weight to the claims. The determination of particular sizes and amounts if within the skill of the ordinary worker as part of the process of normal optimization.

Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant argues that hypothetically combining Trinh with Chen does not teach or suggest the instantly claimed nanoparticles, particularly with the newly added limitations. Applicant argues that combining the references would result in the formation of DOX-cyclodextrin complexes and DOX-cyclodextrin polymer complexes as a control release mechanism to provide a system with optimum release of native DOX, specifically slow release. Applicant further argues that that is not what is instantly claimed, as the instant claims would have different release for the DOX and the cyclodextrin. The examiner is not persuaded by this argument for several reasons. First, discussion of release does not render patentability to the instant claims, as the claims are drawn to compositions. Second, the examiner has relied upon the suggested combination to teach a drug-cyclodextrin complex ion order to modify release of the active from the polymer matrix. Applicant's instant specification states, "complexation of active ingredients with cyclodextrins makes it possible to overcome these disadvantages as it enables the active ingredients to be protected against the outside reaction medium." (p 8, l 16-18). Therefore, Applicant himself teaches that the active and the cyclodextrin will be complexed together. It is unclear to the examiner how the above combination of references really differs from the instant claims, as both teach nanoparticles with a polymer matrix and an active complexed to cyclodextrin. Absent more clear evidenced to the contrary, the examiner maintains her position that the combination of references suggests the limitations of the instant claims. This rejection is maintained.

Claims 1, 2, and 4-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,641,515 to Ramtoola in view of US Patent 5,246,611 to Trinh.

Ramtoola discloses a controlled release pharmaceutical formulation comprising nanoparticles formed of a biodegradable polycyanoacrylate polymer, wherein the active agent is complexed to the polycyanoacrylate. The disclosed particles are capable of releasing the active at a slower release rate than nanoparticles of free active agent (abstract). Ramtoola also teach that the size of the nanoparticles is between 50 and 900 nm (column 2, lines 57-58). Further, Ramtoola teaches that the nanoparticles have a drug loading of 15-25% (abstract).

Ramtoola is discussed as teaching a controlled release formulation of nanoparticles comprising a polycyanoacrylate polymer, and an active, wherein the active is complexed to the polymer. Ramtoola also teaches methods of making the nanoparticles, which suggest applicant's broad process claims.

Ramtoola does not disclose the use of cyclodextrin as a complexing agent. However, Ramtoola does teach that the active agent is complexed to the polymer. It is the position of the examiner that one of ordinary skill in the art would look to the use of a well known complexing agent in order to aid in the complexing of the active agent to the polycyanoactylate polymer.

Trinh discloses cyclodextrin complexes. However, the disclosure of Trinh is relied upon for the teaching that cyclodextrin and its derivatives are very well known to act as complexing agents (c 1, l 25-55). Furthermore, Trinh teaches that the teachings of cyclodextrins inclouds alpha, beta, and gamma-cyclodextrins, and their derivatives, which are all known complexing agents.

It is the position of the examiner that one of ordinary skill in the art would have been motivated to use a cyclodextrin, which Trinh teaches as a well known complexing agent, in the formulation of Ramtoola, which teaches that the active agent is complexed to the polymer. The

expected result would be a successful controlled release nanoparticulate formulation wherein the active agent is complexed to the polycyanoacrylate polymer.

Furthermore, although Ramtoola does not teach the three specifically claimed active ingredients, it is the position of the examiner that applicant has placed no criticality on the specific drug, and therefore any drug could benefit from the controlled release formulation disclosed by Ramtoola. Absent any evidence of criticality, it is the position of the examiner that one of ordinary skill in the art would have been motivated to use any well known drug, which would benefit from controlled release properties, in the formulation disclosed by Ramtoola. The expected result would be a successful controlled release formulation. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant argues that there is no motivation to combine the teachings of Trinh and Ramtoola. The examiner respectfully disagrees, and reasserts that cyclodextrin is a known complexing agent. Yes, it is admitted that Ramtoola teaches the use of another compelxing agent. However, the selection of a known material based on its suitability for its intended use is obvious absent a clear showing of unexpected results azttributatble to the Applicant's specific selection. Therefore, substituting one well known complexing agent for another complexing agent is not patentable, absent specific evidence of unexpected results. For this reasons, this rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E Pulliam whose telephone number is 703-308-4710. The examiner can normally be reached on Mon-Thurs 7:30-5:00, Alternate Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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